REMARKS

Reconsideration is requested.

The Amendment of November 20, 2006 has not been entered. See Advisory Action dated December 8, 2006. The amendment to the specification presented in the Amendment of November 20, 2006 is represented above.

Claims 1-85 have been canceled. Claims 86-105 have been added. The claims have been rewritten as the new claims presented above to avoid any confusion or inconvenience for the Examiner in determining deleted or added text. See Advisory Action and the Examiner's reference to MPEP § 714.II.C.(B). The claims find support throughout the specification. Support for the recited hybridization is found, for example, on page 12, line 34 through page 13, line 7 of the specification. No new matter has been added.

The specification has been revised to include the attached Sequence Listing. The attached paper and computer readable copies of the Sequence Listing are the same. Support for the new SEQ ID NO:38 (the nucleic acid sequence encoding wild-type luciferase of *Photinus pyralis* is found, for example, in SEQ ID NO:1 of U.S. Patent No. 6,265,177, which is derived from International Patent Application No. PCT/GB98/01026 that is explicitly incorporated by reference in the present application at page 12, lines 14-15. No new matter has been added.

The specification has been amended to include a cross-reference to the parent International Application, as may be required according to Rule 78.

Entry of the previously-filed Sequence Listing is acknowledged, with appreciation.

The claims have been amended above to obviate certain formal rejections to at least reduce some issues for appeal.

The claims have been revised to obviate the objection to same stated in Section [10] of the Office Action dated May 16, 2006.

The claims have been revised as suggested by the Examiner in Section [11] of the Office Action dated May 16, 2006.

The Section 112, second paragraph, rejection of claims 79 and 85 is moot in view of the above cancellation of same. The claims have been revised to obviate a similar rejection of same. Specifically, claim 101 recites a comparison step in response to the Examiner's comments contained in Section [12][a] of the Office Action dated May 16, 2006. Moreover, claim 97 (and claim 96) have been drafted in response to the Examiner's suggestions in Section [12][b] of the Office Action dated May 16, 2006. The claims are submitted to be definite.

The Section 112, first paragraph "written description", rejection of claims 67-85 (i.e., stated in ¶[13] on pages 5-7 of the Office Action dated May 16, 2006) is moot. The claims are supported by an adequate written description. Consideration of the following comments in response to the Examiner's rejection of the canceled claims is requested.

The description and claims define that the *Photinus pyralis* luciferase amino acid sequence of SEQ ID NO: 37 as the reference sequence against which the recombinant proteins can be compared. Claim 86, for example, defines a genus encompassing a recombinant protein which has luciferase activity, at least 90% similarity to the *Photinus pyralis* wild-type luciferase of SEQ ID NO: 37, a mutation corresponding to residue 214 of the *Photinus pyralis* luciferase, and increased thermostability compared to the

corresponding wild-type luciferase. Representative examples within the scope of the claimed genus are described in the specification, including recombinant proteins with the following mutations compared to the wild-type *Photinus pyralis* luciferase (of SEQ ID NO: 37):

(1) T214A/I232A/E354K,

(2) T214A/I232A/E354K/A215L,

(3) I232A/E354K/T214A/F295L,

(4) I232A/E354K/T214A,

(5) I232A/E354K/T214A/F295L/F14A/L35A/A215L,

(6) T214A,

(7) T214C, and

(8) T214N, (see page 14, line 28 to page 15, line 9).

Other representative examples of recombinant proteins of the invention are described in Examples 2-4 and 7.

The applicants submit that one of ordinary skill in the art would be aware of wild-type luciferases and that the applicants provide various distinguishing identifying characteristics of the claimed invention relating to structure (i.e. 90% similarity to the luciferase of SEQ ID NO: 37) and biological function (i.e. luciferase function and increased thermostability) of recombinant proteins relating to the *Photinus pyralis* wild-type luciferase. Thus, the ordinarily skilled person with his background knowledge when reading the description and examples of the present application would appreciate that the applicants were in possession of the invention as claimed when the application was filed.

The applicants note that the wild-type firefly luciferases were well characterised at the time the present invention was made, as one of ordinary skill in the art would appreciate. As described in the specification, sequences of many luciferases had already been established (see page 1, lines 16-26 and page 13, lines 20-24). The luciferases show remarkable conservation, especially in key conserved regions of their structure (see Fig. 2 in Ye et al., 1997, Bioch. Biophys Acta 1339: 39-52; of record). Accodingly, there were already natural luciferase variants with high sequence similarity described at the time the present invention was made.

The procedures for making recombinant protein variants, for example variants of the *Photinus pyralis* luciferase of SEQ ID NO: 37, were conventional in the art at the time the present invention was made (see, for example, in EP-A-524448, WO95/25798 and WO96/22376 described in pages 2 and 12 of the specification). Furthermore, assays are described in the specification which will identify such recombinant proteins having the required mutation, luciferase activity and increased thermostability, the required characteristics of the claimed recombinant protein. Moreover, given the high level of skill and knowledge of one of skill in the present art, procedures for making recombinant variants of SEQ ID NO: 37 which have 90% similarity to SEQ ID NO: 37 and which retain luciferase activity but, due to the specified mutation, have higher thermostability, are conventional in the art.

Additionally, the genus of recombinant proteins encompassed by claim 86, for example, does not have substantial variation since all variants must posses at least a specific mutation (corresponding to position 214 in SEQ ID NO: 37), luciferase activity,

increased thermostability and at least 90% similarity to the reference sequence, SEQ ID NO: 37.

Therefore, the several species disclosed are representative of the claimed genus, and one of skill in the art would conclude that the applicants were in possession of the necessary common attributes possessed by members of the genus.

The applicants observe that, according to the USPTO "Revised Interim Written Description Guidelines Training Materials" available on the USPTO website (http://www.uspto.gov/web/offices/pac/writtendesc.pdf), the

> "disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus" (See Example 7: EST, page 31).

The Examiner's attention is further drawn to the following Example 14 of the Training Materials, in which the exemplar claim is directed to a protein having a specific sequence and variants thereof with at least 95% identity to that sequence and capable of catalysing a specific biological reaction:

> **"Example 14: Product by Function**
> **Specification:** The specification exemplifies a protein isolated from liver that catalyzes the reaction of **A→ B.** The isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO: 3. The specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following:
> substitutions, deletions, insertions and additions. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.
> **Claim:**

A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A →B.

Analysis:

A review of the full content of the specification indicates that a protein having SEQ ID NO: 3 or variants having 95% identity to SEQ ID NO: 3 and having catalytic activity are essential to the operation of the claimed invention. The procedures for making variants of SEQ ID NO: 3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO: 3 which have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art. A review of the claim indicates that variants of SEQ ID NO: 3 include but are not limited to those variants of SEQ ID NO: 3 with substitutions, deletions, insertions and additions; but all variants must possess the specified catalytic activity and must have at least 95% identity to the SEQ ID NO: 3.

Additionally, the claim is drawn to a protein which **comprises** SEQ ID NO: 3 or a variant thereof that has 95% identity to SEQ ID NO: 3. In other words, the protein claimed may be larger than SEQ ID NO: 3 or its variant with 95% identity to SEQ ID NO: 3. It should be noted that "having" is open language, equivalent to "comprising". The claim has two different generic embodiments, the first being a protein which comprises SEQ ID NO: 3 and the second being variants of SEQ ID NO: 3. There is a single species disclosed, that species being SEQ ID NO: 3.

A search of the prior art indicates that SEQ ID NO: 3 is novel and unobvious. There is actual reduction to practice of the single disclosed species.

The specification indicates that the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO: 3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.

Conclusion: The disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention.

The example provides that there is reduction to practice of the single disclosed species but that the claimed variants are contemplated but not exemplified. Yet the applicant is deemed to be in possession of the invention because the single species is representative of the claimed genus, all members of the genus must have a given structural identity to the given sequence, and there is an assay which would identify all of the claimed variants.

By analogy with Example 14, the applicants submit that the present specification similarly provides an adequate written description, from which one of ordinary skill in the art would conclude that the applicants were in possession of the invention recited in the claims.

The applicants note that the term "similarity" is recited in the claims, which one of ordinary skill in the art will appreciate from the specification refers to a quantifiable parameter which involves measurement of sequence similarity between a recombinant protein and the wild-type luciferase of SEQ ID NO: 37 referred to in the claims. In the present application at page 13, lines 9 - 24, it is stated that sequence similarity may in particular be assessed (i.e. quantified) using the well-known Lipman and Pearson (1985) multiple alignment method, and the exact parameters which should be used in determination of similarity are provided. An ordinarily skilled person comparing an "unknown" sequence with the reference sequence of SEQ ID NO: 37 would, using the Lipman and Pearson method referred to in the application, arrive at only one value of sequence similarity and be able to determine whether or not the unknown sequence fell with the scope of the claims.

The Examiner has dismissed the applicants' comparison of the present facts with the guidance of the above PTO Example 14 as the Examiner notes that

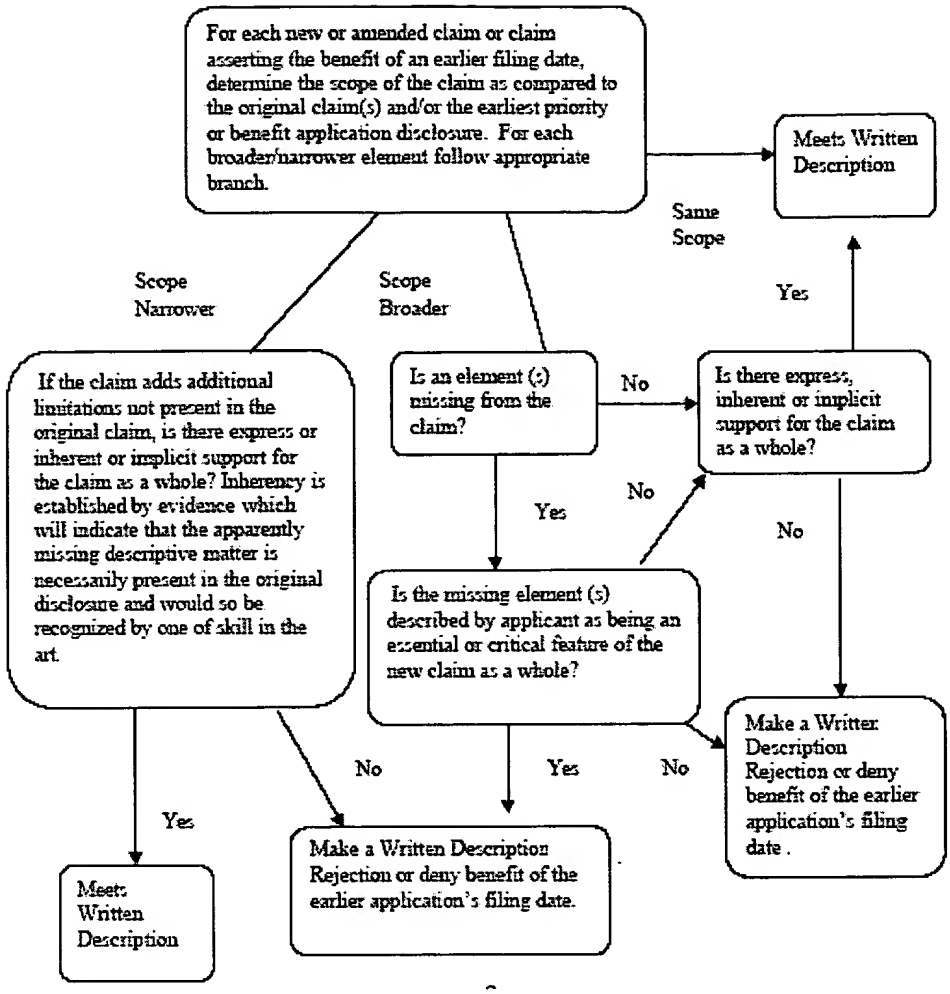
> "there are at least two differences between the Example 14 claim and the instant claims: 1) the number limitation, *i.e.*, 90% and 95%, and 2) the method of sequence comparison, *i.e.*, identity and similarity. Thus, contrary to applicant's argument, the instant claims are not analogous to Example 14 of the Guidelines." See, page 6 of the Office Action dated May 16, 2006.

The applicants submit, with due respect to the Examiner, that there is no indication in the Training Materials, or elsewhere, that the guidance of Example 14 is based on the recitations of 95% and "identity". The Examiner will appreciate that "analogous" elements, traits, structures, etc. are often dissimilar in some respects. See http://www.google.com/search?hl=en&lr=&rls=com.microsoft:en-US&defl=en&q=define:analogous&sa=X&oi=glossary_definition&ct=title ("similar or equivalent in some respects though otherwise dissimilar; "brains and computers are often considered analogous"; "salmon roe is marketed as analogous to caviar" "; "An analogy is a comparison between two different things, in order to highlight some form of similarity." (emphasis added)).

The Examiner's apparent focus on whether the "claims" of the present application are analogous to the claim of Example 14 is submitted, again with due respect to the Examiner, to be too narrow. The focus of the written description requirement is whether the specification describes the claimed invention in the context of the level of technical ability and knowledge of one of skill in the art. The focus of the Examples in the Training Materials is based on a determination of whether the specification in each fact hypothetical supports the claimed invention. In Example 14 of the Training Materials,

the claim defined a protein having a give sequence (i.e., SEQ ID NO: 3) or variants having 95% identity to that sequence. Although Example 14 does not specifically provide a complete description of the hypothetical specification, it is likely that the specification did not include a comparison of the sequences based on "similarity" but the applicants in that hypothetical chose to describe their invention in terms of identity. Moreover, although there is no certainty, it is likely that the hypothetical applicants in the specification of Example 14 of the Training Materials chose to describe their variants as having 95% identity to the base sequence. The fact however that the PTO hypothetical claim and specification of Example 14 uses the terms "identical" and "95%" does not limit the applicability of the Training Materials to an analogous fact scenario, such as is presented by the present claims and the present specification, to determine that the present claims are supported by an adequate written description.

The applicants further note that the Training Materials provide the following "Decision Tree" for determining whether the claims of an application are supported by an adequate written description:



The first step of this "decision Tree" involves determining the scope of the claims as compared to the original claims.

The applicants believe that claim 86 is similar to claim 1 as originally filed except for the further limitations of (1) being a recombinant protein, (2) the recitation regarding sequence similarity (i.e., "at least 60%" in originally-filed claim 1 and "at least 90% similar" in claim 86), and (3) being a mutated wild-type sequence.

The Decision Tree indicates that where amended claims add additional limitations not present in the original claims, the Examiner is to determine if there is

express or inherent support for the claim as a whole and if so then the claims "meets written description" (i.e., the claims are supported by an adequate written description).

The present specification describes on page 1, lines 28-32 and page 12, lines 21-22, for example, that the proteins of the invention may be recombinant proteins.

Moreover, the specification describes, for example, at page 12, lines 21-32, that the proteins of the invention can be at least 90% similar to the wild-type base sequence. As noted above, sources of similarity algorithms are described in the specification on page 13, lines 9-24.

Finally, the present specification describes on page 13, lines 26-29, that proteins of the invention can include mutated wild-type sequences.

According to the Decision Tree, the specification provides an adequate written description of the invention of claim 86.

Claim 91 is dependent on claim 86 and describes a further aspect of the invention which is similar to the originally-filed claim 2, which was dependent from claim 1 of the originally-filed application. As claim 91 differs from originally-filed claim 2 in the aspects described above with regard to the comparison between independent claims 86 and originally-filed claim 1, claim 91 is believed to be adequately described by the specification according to the analysis of the Decision Tree.

Claim 92 is dependent on claim 86 and describes a further aspect of the invention which is similar to the originally-filed claim 3, which was dependent from claim 2 of the originally-filed application. As claim 92 differs from originally-filed claim 3 in the aspects described above with regard to the comparison between independent claims 86

and originally-filed claim 1, claim 92 is believed to be adequately described by the specification according to the analysis of the Decision Tree.

Claim 93 is dependent on claim 86 and describes a further aspect of the invention which is similar to the originally-filed claim 4, which was dependent from any one of claims 1-3 of the originally-filed application. As claim 93 differs from originally-filed claim 4 in the aspects described above with regard to the comparison between independent claims 86 and originally-filed claim 1, claim 93 is believed to be adequately described by the specification according to the analysis of the Decision Tree.

Claim 94 is dependent on claim 86 and describes a further aspect of the invention which is similar to the originally-filed claim 8, which was dependent from claim 1 of the originally-filed application. As claim 94 differs from originally-filed claim 8 in the aspects described above with regard to the comparison between independent claims 86 and originally-filed claim 1, claim 94 is believed to be adequately described by the specification according to the analysis of the Decision Tree.

Claim 95 is dependent on claim 86 and describe a further aspect of the invention which is similar to the originally-filed claim 21, which was dependent from any of claims 1-20 of the originally-filed application. As claim 95 differs from originally-filed claim 21 in the aspects described above with regard to the comparison between independent claims 86 and originally-filed claim 1, claim 92 is believed to be adequately described by the specification according to the analysis of the Decision Tree.

Claim 96 is dependent on claims 95, and describes a further aspect of the invention which is similar to the originally-filed claim 22, which was dependent from claim 21 of the originally-filed application. As claim 96 differs from originally-filed claim

22 in the aspects described above with regard to the comparison between independent claims 86 and originally-filed claim 1, claim 96 is believed to be adequately described by the specification according to the analysis of the Decision Tree.

Claim 97 is dependent on claim 96, and describes a further aspect of the invention which is similar to the originally-filed claim 23, which was dependent from claim 22 of the originally-filed application. As claim 97 differs from originally-filed claim 23 in the aspects described above with regard to the comparison between independent claims 86 and originally-filed claim 1, claim 97 is believed to be adequately described by the specification according to the analysis of the Decision Tree.

Claim 98 is dependent on claim 97 and describes a further aspect of the invention which is similar to the originally-filed claim 24, which was dependent from claim 23 of the originally-filed application. As claim 98 differs from originally-filed claim 24 in the aspects described above with regard to the comparison between independent claims 86 and originally-filed claim 1, claim 98 is believed to be adequately described by the specification according to the analysis of the Decision Tree.

Claim 99 is dependent on claim 97 and describes a further aspect of the invention which is similar to the originally-filed claim 25, which was dependent from claim 23 of the originally-filed application. As claim 99 differs from originally-filed claim 25 in the aspects described above with regard to the comparison between independent claims 86 and originally-filed claim 1, claim 99 is believed to be adequately described by the specification according to the analysis of the Decision Tree.

Claim 100 is dependent on claim 99 and describes a further aspect of the invention which is similar to the originally-filed claim 26, which was dependent from

claim 25 of the originally-filed application. As claim 100 differs from originally-filed claim 26 in the aspects described above with regard to the comparison between independent claims 86 and originally-filed claim 1, claim 100 is believed to be adequately described by the specification according to the analysis of the Decision Tree.

Claim 101 is similar to originally-filed "use" claim 28, which was dependent on originally-filed claims 1-20. The following additional recitations are included as aspects of claim 101, as compared to originally-claimed 28: (1) that a bioluminescent assay comprises luciferase/luciferin reaction and detection of bioluminescence, and (2) that the protein according to the invention provides an improvement as compared with the corresponding wild-type luciferase in the reaction.

The specification describes on pages 1 and 2, for example, that a bioluminescent assay comprises luciferase/luciferin reaction and detection of bioluminescence. The applicants believe this aspect of bioluminescent assays were well known such that the same was not only specifically, but also inherently, disclosed in the present specification.

The specification further describes, for example, in the paragraph spanning pages 1 and 2, that the present invention provides an advantage in a bioluminescent assay, for example, which is effected under high temperature reaction conditions, for example in order to increase reaction rate.

According to the Decision Tree, the specification provides an adequate written description of the invention of claim 101.

Claim 102 is dependent on claim 86 and describes a further aspect of the invention which is similar to the originally-filed claim 29, which was dependent from any

one of claims 1 to 20 of the originally-filed application. As claim 102 differs from originally-filed claim 29 in the aspects described above with regard to the comparison between independent claims 86 and originally-filed claim 1, claim 102 is believed to be adequately described by the specification according to the analysis of the Decision Tree.

Claim 103 is dependent on claim 102 and describes a further aspect of the invention which is similar to the originally-filed claim 30, which was dependent from claim 29 of the originally-filed application. As claim 103 differs from originally-filed claim 29 in the aspects described above with regard to the comparison between independent claims 86 and originally-filed claim 1, claim 103 is believed to be adequately described by the specification according to the analysis of the Decision Tree.

Claims 87 and 88 are similar to claim 1 of the originally-filed specification. Claims 87 and 88, like claim 86 additionally describes the claimed protein as being recombinant. As noted above, the specification describes, for example, at page 1, lines 28-32 and page 12, lines 21-22, that the proteins of the invention include recombinant proteins. Claims 87 and 88 additionally describe the claimed protein as not containing Thr at the residue corresponding to residue 214 of the *Photinus pyralis* wild-type sequence described at page 12, lines 14-15 of the specification See page 3, ¶[8] of the Office Action dated May 16, 2006. Moreover, claims 87 and 88 additionally describe the claimed protein with reference to hybridization conditions described, for example, in the paragraph spanning pages 12-13 of the specification. According to the Decision Tree, the applicants believe the specification provides an adequate written description of the invention of claims 104 and 108.

Claims 89 and 90, which are dependent from claims 87 and 88, respectively, additionally define the claimed proteins as including a specifically recited amino acid in place of the amino acid corresponding to the Thr-214 of the *Photinus pyralis* wild-type sequence. This aspect of the claimed invention is described, for example, at page 7, lines 26-36 of the specification. According to the Decision Tree, the applicants believe the specification provides an adequate written description of the invention of claims 89 and 90.

Claim 104 is similar to originally-filed claims 1 and 7. Like claim 86, claim 104 defines the claimed protein as being a recombinant protein, as described in the previously-noted passage of the specification. Claim 104 does not include the percent similarity recitation of originally-filed claims 1 and 7 and in this aspect is more limited. The specification further describes the additional aspects of claim 104 at page 12, lines 21-32 and page 7, lines 26-36. According to the Decision Tree, the applicants believe the specification provides an adequate written description of the invention of claim 104.

Claim 105 is dependent on claim 104 and additionally includes recitations further described on page 14, line 28 to page 15, line 9 as well as Examples 2-4 and 7 of the specification.

The claims are submitted to be supported by an adequate written description.

The Section 112, first paragraph "enablement", rejection of claims 67-85 is moot. The claims are submitted to be supported by an enabling disclosure. Consideration of the following in this regard is requested.

Independent claim 86 describes recombinant proteins with at least a specific mutation corresponding to position 214 of SEQ ID NO:37, luciferase activity, increased

thermostability and at least 90% similarity compared to SEQ ID NO: 37. As mentioned above, numerous representative examples within the scope of the claims are provided in the specification, and the applicants also provide clear teaching and guidance on how to make, test and use other species of recombinant proteins within the scope of the claims. The applicants submit that the amended claims are enabled.

The Examiner has referred to MPEP 2164.03 regarding predictability. However, in assessing enablement, MPEP 2164.01(a) also notes that the Examiner should consider several factors, including the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. The Manual states that it is improper to conclude that a disclosure is not enabling based in an analysis of only one of the above factors while ignoring one or more of the others. The Examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. This has been reinforced by the recent decision of Capon v. Eshhar v. Dudas (US Court of Appeals for the Federal Circuit, 12 August 2005), where the court stated that the determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter.

The applicants request that the Examiner takes into account all of the relevant factors regarding enablement and to not, for example, focus on only the aspect of predictability. Inventions in the biological sciences, for instance relating to recombinant proteins, may contain an amount of some unpredictability however if the same were an absolute bar to patentability, then it may not be possible for an applicant or patentee to claim a variant of a specific protein sequence by sequence identity or similarity variation. This would be contrary to the Patent Office practice, as evidenced by previously granted U.S. patent claims and the Training Materials of the USPTO (see for example, Example 14 of the USPTO "Revised Interim Written Description Guidelines Training Materials" mentioned above). With sufficient teaching in the specification on how to make and test variants, as has been provided in the present application, there is no undue experimentation required by one of ordinary skill to make and use the full scope of the claimed invention. The applicants therefore respectfully submit that the application, as directed to one of ordinary skill and taking into account the state of the prior art, provides enablement for the claimed invention.

The provisional obviousness-type double patenting rejection of claims 67-85 over claims 1-4, 6-10, 14, 17-19 and "6-23" of copending Application Serial No. 10/111,723 is moot in view of the above.

The claims are submitted to be in condition for allowance and notification of the same is requested. Once allowable subject matter is indicated, the applicants will be able to assess the appropriateness of the provisional obviousness-type double patenting rejection.

Respectfully submitted,

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